

# Statistical Considerations'

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## Disclosure

No disclosures

## Statistical Considerations

- Consideration of Using a Single-Arm Trial Design, and the Final Randomized Trial Design Considerations
- Sample Size Determination and Group Sequential Analyses
- Patient Eligibility Changes and Final Analysis Considerations

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## Multivariable Models of Restenosis

<u>Model A</u>	<u>Odds Ratio</u>	<u>p-value</u>
Post-Proc In-Stent MLD (per mm)	0.32	<0.001
* Lesion Length (per mm)	1.03	0.005
Diabetes mellitus	1.48	0.033
<u>Model B</u>		
Post-Proc In-Stent MLD (per mm)	0.33	<0.001
Diabetes mellitus	1.54	0.018
* Stent Length (per mm)	1.02	0.040

\* Lesion Length and Stent Length are collinear.

## Predictors of Clinical Restenosis

### *Multivariable predictors of TLR*

<u>Variable</u>	<u>Odds Ratio (95% CI)</u>	<u>p</u>
Final MLD (per mm)	0.31 (0.24-0.40)	0.0001
Stent length (per mm)	1.02 (1.01-1.03)	0.0001
Prior MI	0.64 (0.51-0.80)	0.0001
Diabetes Mellitus	1.40 (1.11-1.77)	0.005
Unstable angina	1.33 (1.07-1.65)	0.008
Cigarette smoking	0.80 (0.64-0.99)	0.047

After adjustment for these variables, pre MLD ( $p>0.10$ ), final dissection ( $p=0.06$ ), LAD ( $p>0.10$ ), multivessel disease ( $p=0.06$ ), and hypertension ( $p>0.10$ ) were not significant predictors

## Predicted Angiographic Restenosis Rates

Post-Procedure In-Stent MLD	Lesion Length			
	10 mm	15 mm	20 mm	25 mm
<i>Diabetics</i>				
2.5 mm	35%	39%	43%	46%
3.0 mm	23%	26%	30%	33%
3.5 mm	15%	17%	19%	22%
4.0 mm	9%	10%	12%	14%
<i>Non-Diabetics</i>				
2.5 mm	27%	30%	33%	37%
3.0 mm	17%	19%	22%	25%
3.5 mm	10%	12%	14%	16%
4.0 mm	6%	7%	8%	10%

## Using Bayesian Techniques: *Comparing New Stent Registry Data with Prior RCT Pool*

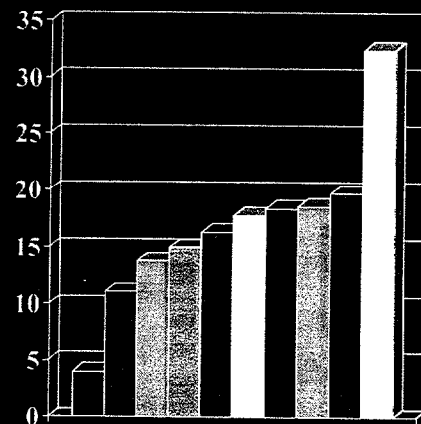
- Use results from multiple stent RCTs as prior
  - RCTs should be FDA approved
  - Data already exist
- Create a model that predicts the outcome of interest
  - Use proper Bayesian/meta-analytical techniques for combining data and weighting trial results
  - Develop a predictor model of the outcome based on conventional and database unique factors
    - Improve  $\beta$  coeff. estimates with latent variable prediction models
- Conduct a single arm study of new stent

## Using Bayesian Techniques: *Comparing New Stent Registry Data with Prior RCT pool (continued)*

- Predict the outcome from the pooled dataset based on the adjusted model
- Compare the estimates
  - OPC vs new data
  - OPC has proper variance
- Approve stent based on test hypothesis
  - Use non-inferiority testing hypotheses for new standard stents
  - Use superiority testing hypotheses for anti-restenosis strategies such as stents plus drug coatings or adjunctive treatments.

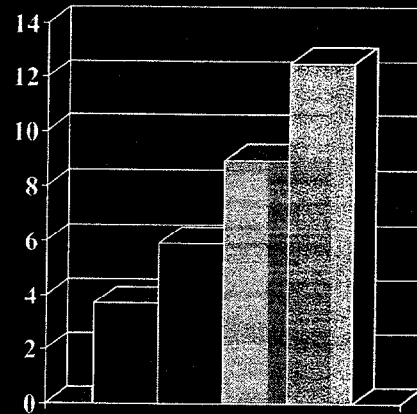
## MACE Estimates of SVG Intervention from Historical Controls

- No Protection
  - SAVED: <4%
  - SAFER-1: 11.1%
  - Caveat-II: 13.2%
  - Hong: 15%
  - Ellis No Abcix: 16.3%
  - BIDMC: 17.8%
  - RAVES: 18.4%
  - Ellis Abcix: 18.6%
  - SAFER-2: 19.7%
  - VeGAS 2: 32.5%



## MACE Estimates of SVG Intervention from PercuSurge Trials

- Protection (PercuSurge)
  - Webb: 3.7%
  - SAFE: 5.9%
  - Safer 2<sup>nd</sup> Cohort: 9.0%
  - Safer 1<sup>st</sup> Cohort: 12.5%



## OPCs and SVG Device Evaluation

- The wide range of vein graft clinical outcomes following catheter-based therapies requires case-mix adjustment for precise expected outcome predictions.
- The lack of current scalable covariates on which to build a predictors models makes derivation of a precise expected outcome impossible.
- Randomized trials are critical for the evaluation of SVG devices.

## Statistical Considerations

• How to develop a Sample Size and Design and the Final Randomized Trial  
• Design Considerations

- Sample Size Determination and Group Sequential Analyses

• How to develop a Sample Size and Design  
• Design Considerations

## Statistical Analysis Plan

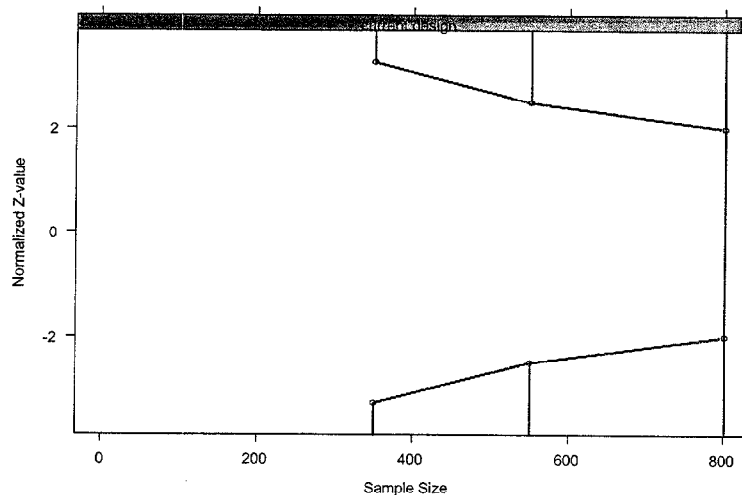
- Estimate of Control rate = 16.0%
- Treatment Rate: 9.0%
- Alpha error: 5%
- Power 80%
- Group sequential analysis
  - 2 interim looks and final analysis

## Group Sequential Analysis Plan: Intended Design

N=	0	100	200	300	400	500	600	700	800
Nominal p-value (Geller Pocock 1987)				267		533		800	
				0.014		0.021		0.026	
Actual interim points G/P p-value				350		550		800	
				0.014		0.021		0.030	
(Wang & Tsiatis 1987)									
boundary shape "0.6"				0.019		0.026		0.031	
(Lan & DeMets 1983)				0.019		0.020		0.030	

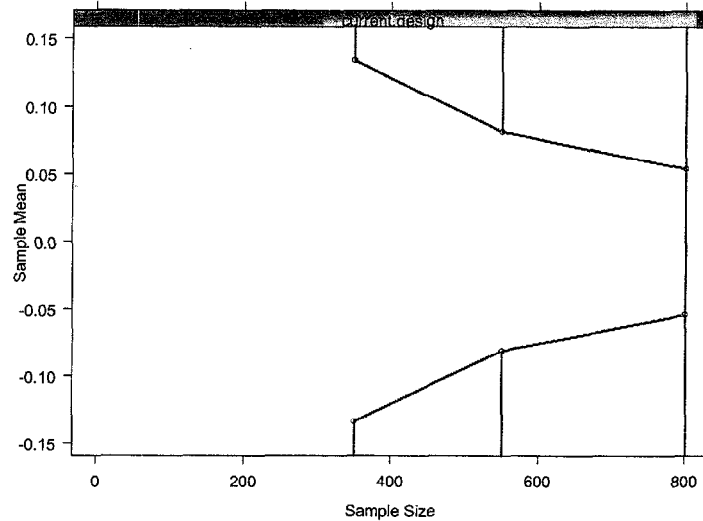
## Boundary Conditions

Normalized Z-Value for 350, 550, and 800 Patients



## Boundary Conditions

Sample Mean Difference for 350, 550, and 800 Patients



## SAFER patient enrollment

- Learning cases: up to 10 cases per center
  - Total: 303 at 68 sites
  - Average per center: 4.5 patients
  - Range: 2-9
- Study approved for up to 800 randomized cases (Total: 801)
- Interim stopping rules approved for 350 and 550 patient intervals

## Statistical Considerations

- Patient Eligibility Changes and Final Analysis Considerations

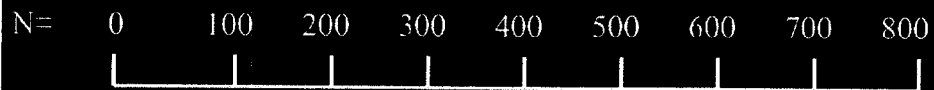
### Group Sequential Analysis Plan: Analytical Considerations



Nominal p-value                      0.014                      0.021                      0.026  
(Geller Pocock 1987)

RCT \_\_\_\_\_  
N=801

## Group Sequential Analysis Plan: Analytical Considerations



Nominal p-value (Geller Pocock 1987)

	0.014	0.021	0.026
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RCT  
N=801

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0            142

Slow enrollment, criteria widened

## INCLUSION EXPANSION

Original	Final
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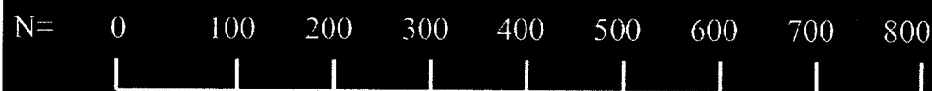
- 2 Discrete Lesions
- Staging of coronary cases only after 30 days
- CK levels normal for 72 hours
- TEC excluded

***Result: Restricted cohort  
and slow enrollment***

- Multiple lesions and diffuse disease
- Staging of coronary cases allowed
- CK levels normal for 24 hours
- TEC included

***Result: More complex lesions  
at higher risk, much faster  
enrollment***

## Group Sequential Analysis Plan: Analytical Considerations



Nominal p-value (Geller Pocock 1987)

Nominal p-value	0.14	0.21	0.26
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RCT  
N=801

0 142

Slow enrollment, criteria widened

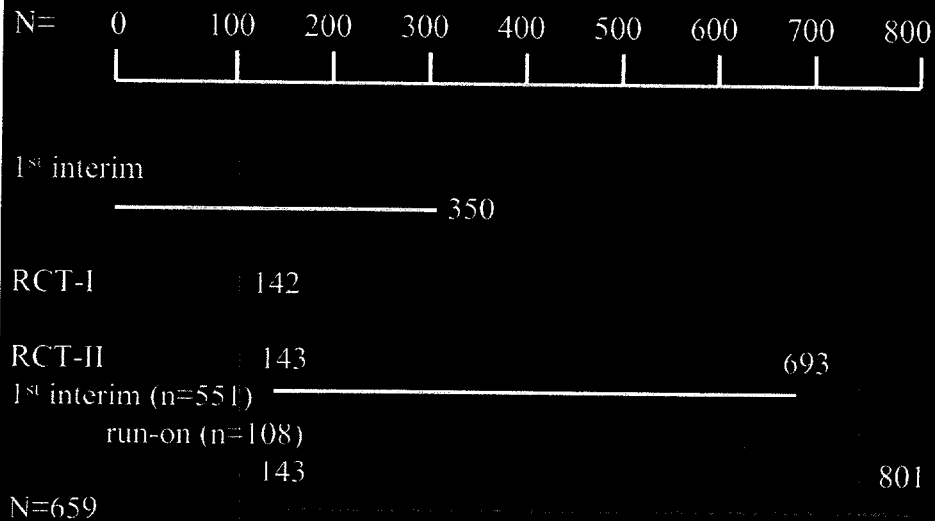
1<sup>st</sup> interim

350

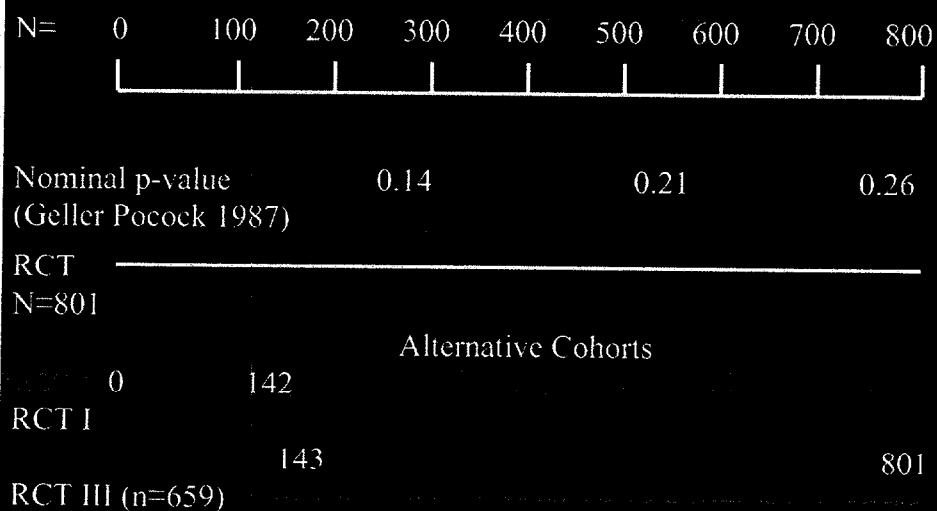
## Consideration for a New Analyzable Cohort

- *1st interim analysis* DSMB: "Continue trial"
- Sponsor: "Did restricted eligibility period reduce control rate below 16%?" (remained blinded to data)
- Consulted CDAC, DSMB, FDA
  - Statistical review by S. Pocock, J Orav (DSMB statistician, FDA statisticians)
  - FDA consultation: agreed with logic but no guarantees
- Considered virtual restarting of new trial at point of new enrollment criterion (pt 143)
- Re-start analysis at patient 143.
  - 1<sup>st</sup> new interim analysis at 550, not 350
  - Alpha error expenditure charged for re-starting
- Practically, a new 550 interim review and conclusion would be reached after the all 800 patients were enrolled.

## Group Sequential Analysis Plan: Alternative Cohorts



## Group Sequential Analysis Plan: Analytical Considerations

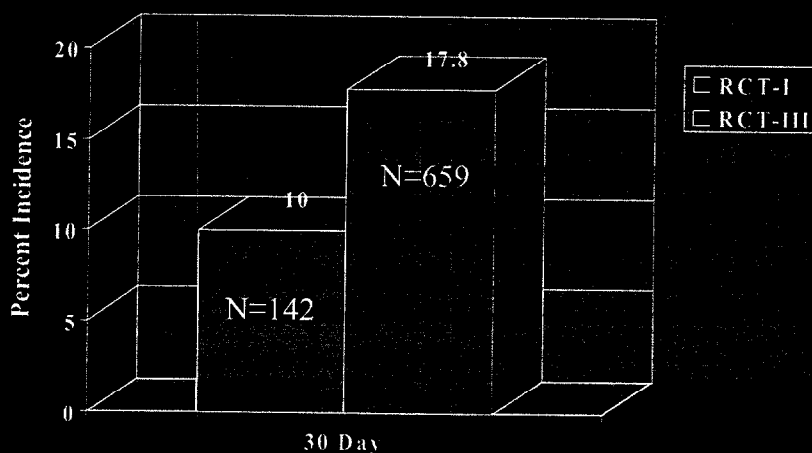


## Consideration for a New Analyzable Cohort

- **FDA position:** Analysis of new cohort would be considered but not guaranteed.
- **Statistical considerations:**
  - Evaluate total 801 patients using final nominal p-value of 0.03
    - In this case, trial is completed as planned.
    - Overall p-value was attained (43% treatment effect,  $p=0.004$ ).
  - Evaluate the 659 patients cohort using the nominal p-value of 0.02.
    - In this case, treatment difference estimates (49% treatment effect,  $p=0.001$ ) might better reflect the utility of the device in patients with broad criteria.
    - Interim 551 patient nominal p-value was attained (50% treatment effect,  $p=0.001$ ).

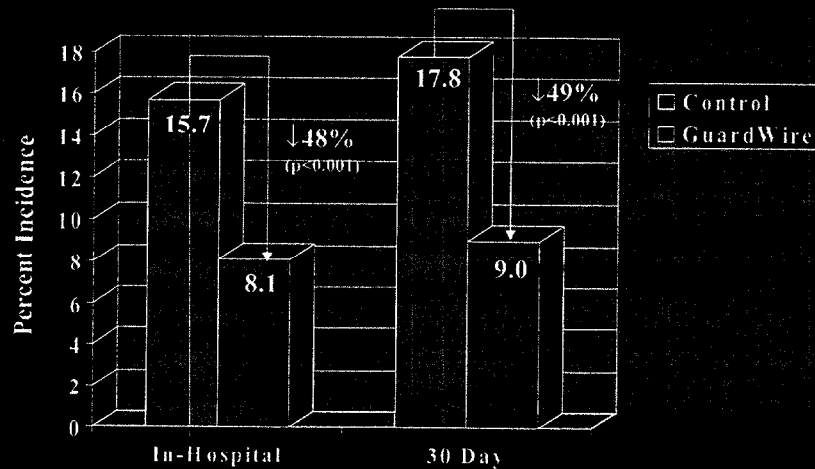
## The SAFER Trial

*MACE for Control Arms in the 1<sup>st</sup> and 2<sup>nd</sup> Cohorts*



## The SAFER Trial

### MACE for 2<sup>nd</sup> Cohort of 659 patients



## Conclusions

The 659 patient cohort, which had broad eligibility criteria and rapid enrollment, best represents patients with vein graft disease, and provides the best dataset in which to estimate the difference in MACE between the two arms.